Original Article

Molecular docking study of natural compounds as cyclooxygenase-2 inhibitors

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ABSTRACT

Natural compounds have been found to possess the anti-inflammatory properties. The study aimed to look for the possible of the natural compounds belonging to alkaloid, phenolic, flavonoids, and terpenoids by docking study with the target protein, cyclooxygenase-2 (COX-2). Crystal structure of COX-2 was retrieved from RCSB Protein Data Bank. Docking study was performed with the help of Auto Dock Vina. Docking study showed that the compounds belonging to alkaloid group, that is, rutaecarpine and tryptanthrine were found to possess high binding energy. Selective COX-2 best known for their anti-inflammatory properties act by blocking COX-2 enzymes suggests the natural compounds exhibited the anti-inflammatory properties by eliminating the signs and symptoms of inflammation.

Keywords: Nonsteroidal anti-inflammatory drugs, anti-inflammatory, cyclooxygenase-2 enzyme, molecular docking

INTRODUCTION

Cyclooxygenase (COX) is a family of isozymes that is responsible for the catalysis of the reaction involving arachidonic acid to form various prostaglandins and related compounds.[1] Till now, there are mainly two identified isoforms of the COX enzyme, namely, COX-1 and COX-2. COX-1 serves a homeostatic function in most tissues where it is constitutively present and has housekeeping function and under normal physiological conditions, it exhibits cytoprotective action along with regulation of platelet activity, renal and gastric functions. COX-2 is usually found in cells where an increased level of prostaglandin is observed during inflammatory reactions. COX-2 is induced due to inflammatory stimuli and does not have a constitutive presence like COX-1. The different model showed that deletion of COX-2 gene independent of the immune response significantly contributed to suppression of the pathogenesis of inflammation. This suggests the presence of complex regulatory pathways in the induction of pain and its causative reason.[2] Earlier the steroidal anti-inflammatory drugs were used in the treatment of inflammation but due to the serious adverse effect of steroidal anti-inflammatory drugs, their use for treatment decreased gradually. To overcome these problems, nonsteroidal anti-inflammatory drugs (NSAIDs) were introduced in the market with fewer adverse effects or other side effects such as renal impairment and gastric ulcers. The COX-2 is an inducible isoenzyme that is responsible for the formation of inflammatory prostaglandins. Therefore, selective COX-2 inhibitors were launched in the market with less or no gastric ulcer risk.[3-7]

Apart from the marketed compounds, natural compounds (rutaecarpine, tryptanthrine, isolicoflavonol, lonchocarpol A, curcumin, resveratrol, and ursolic acid)[8-13] as a selective COX-2 inhibitors are also been used for the management of inflammation. No comparative studies using *in silico* approaches have yet been reported for these compounds. The use of *in silico* approaches has provided the opportunity to study the interaction at the molecular level. The study aimed to explore the possible anti-inflammatory activity of the compound by docking study against target protein COX-2.

MATERIALS AND METHODS

Preparation of protein molecule

COX-2 complexed with the celecoxib (selective inhibitor (Protein Data Bank [PDB] ID: 3LN1)[14] retrieved from RCSB PDB (https://

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www.rcsb.org/pdb/) as a PDB file. The cocrystal selective inhibitor was removed to get native target protein. The target protein COX-2 is a homodimer comprising two identical chains A and B with similar active site. Protein was prepared using Auto Dock Tools (ADT) 4.2.6.[15] In protein preparation, A chain, all water molecules and heteromolecule of 3LN1 were deleted. Polar hydrogen and Kollman charges were added and then protein is saved in pdbqt form.

Preparation of ligand

The structure of all the ligand is drawn in ChemDraw and the energy minimization is done using Chem 3D and the file is saved in PDB format. The PDB file is converted into pdbqt format using ADT. In ligand preparation, Gasteiger partial charges were assigned and non-polar hydrogen atoms were merged.

Docking

Docking study was performed to check the binding affinity of ligands with the COX active site residue of COX-2 enzyme (PDB ID: 3LN1) using the software Auto Dock Vina. A grid box covering the COX active residue of the target protein was generated to get the best conformation state of docking. Docking grid box was set to 30 × 30 × 30 Å dimension, spacing of 0.375 Å and centered at 31.724, –22.0063. –17.132 of X,Y, and Z coordinate. Docking was performed using Auto Dock Vina.

RESULTS AND DISCUSSION

Before performing the docking study, the docking protocol was validated. The cocrystal celecoxib was removed from the protein and again docked back into the active site of COX-2. The 2D interaction was generated using discovery studio (Dassault Systemes Biovia Corp). Root mean square deviation of the protein in cocrystal complex formation and the best docked conformation was zero. Ligand showed deviation which was negligible. This indicated the ability of the docking protocol to reproduce the binding mode of the cocrystal inhibitor. In the docking study, the celecoxib showed interaction with LEU345, VAL335, ALA513, TRP373, GLY512, TYR371, TYR341, VAL509, SER339, ARG449, HIS75, GLN178, LEU338, and PHE504. The H-bond interaction is observed between the sulfonyl group and SER339, ARG449, HIS75, and PHE504 while NH group and HIS75, LEU338, and GLN178 also possessed the H-bond interaction. The other interaction like amide pi stacked is observed between sulfophenyl group and SER339 and VAL509. The celecoxib also showed pi-sigma carbon hydrogen bond, alkyl, and pi alkyl with TYR341, LEU345, VAL335, ALA513, GLY512, TYR371, and TRP373 at the A chain of active site of COX-2. The interaction of the celecoxib with the COX-2 receptor is shown in Figure 1.

The present docking study showed that the natural compounds favorably fit in the active site of COX-2 with

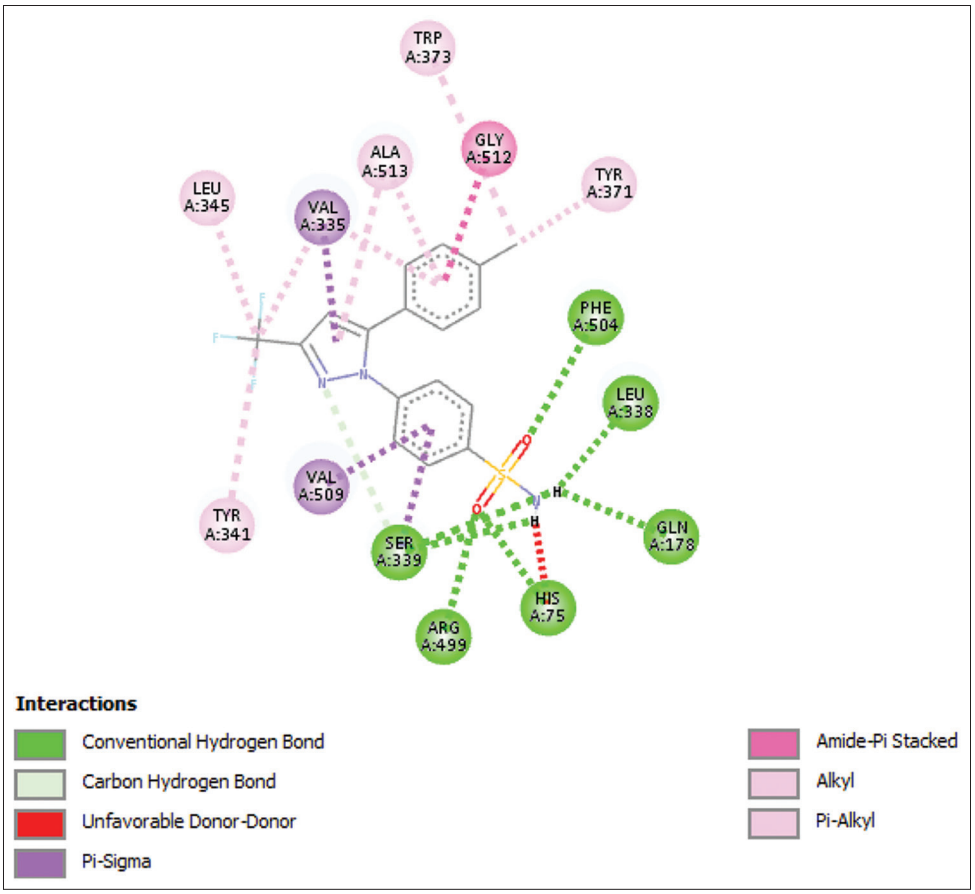


Figure 1: The interaction of the celecoxib with the cyclooxygenase-2 receptorc

maximum up to –11.0 kcal/mol and minimum up to –6.8 kcal/mol of flavonoid (lonchocarpol A) which was comparable to celecoxib with binding energy of –12.2 kcal/mol. Although the highest binding energy is possessed by the alkaloid (rutaecarpine and tryptanthrine) [Figures 2 and 3], the maximum interaction with COX-2 is possessed by the curcumin which has binding energy of –9.1 kcal/mol. The minimum interaction is showed by the lonchocarpol A and ursolic acid (binding energy = –8.5 kcal/mol). The binding energy of the ligand along with the amino acids involved in the interaction is mentioned in Table 1.

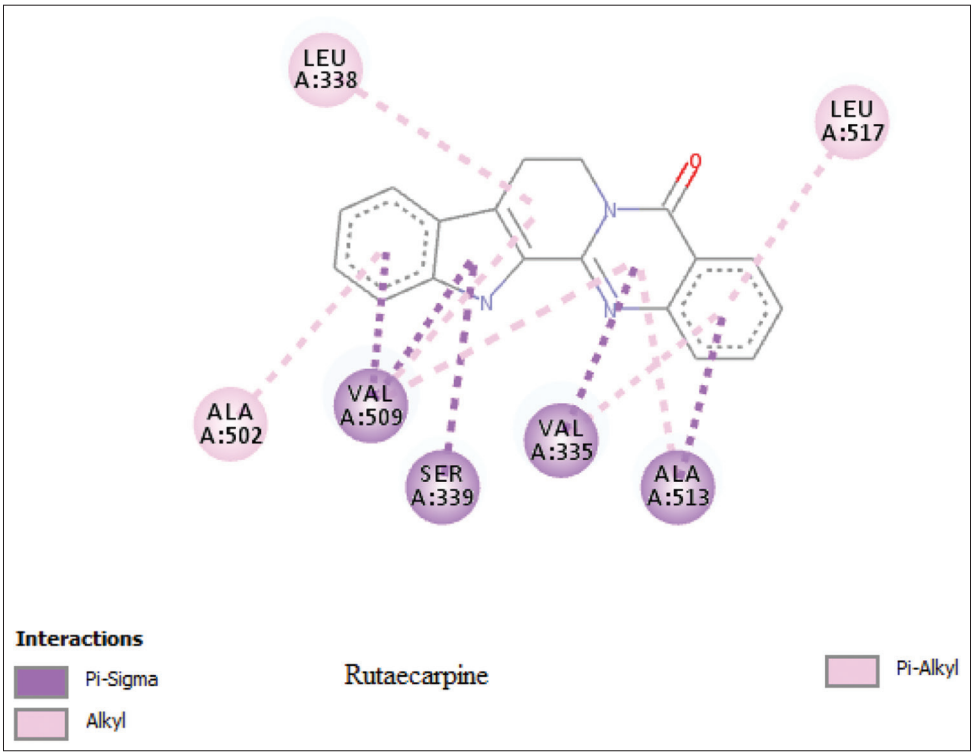


Figure 2: The interaction of rutaecarpine at cyclooxygenase-2

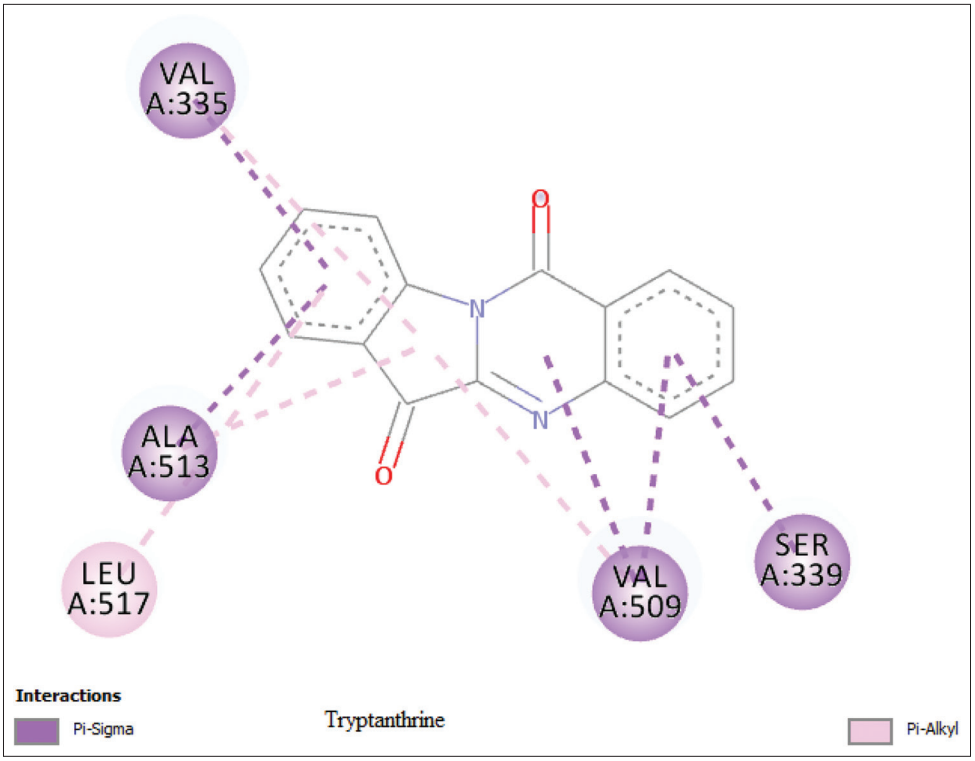
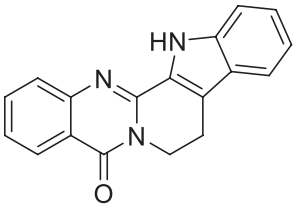
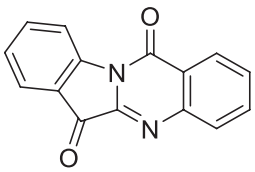
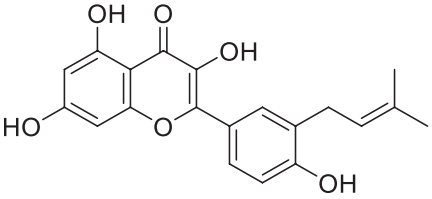
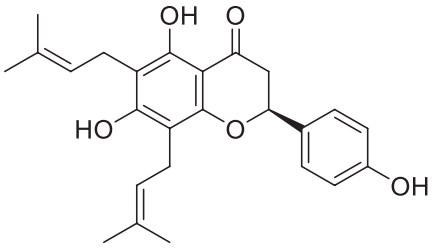
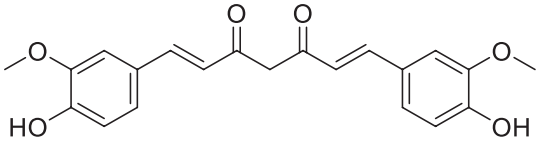
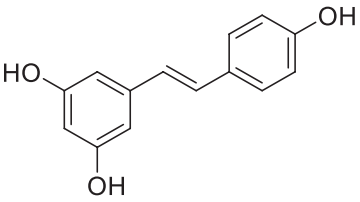
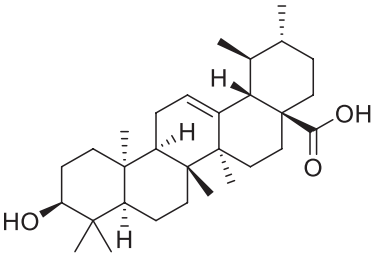
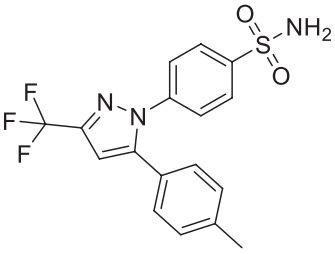


Figure 3: The interaction of tryptanthrine at cyclooxygenase-2

Table 1:The binding energy of the ligand along with the amino acids involved in the interaction

S. No.	Compounds	Structure	Binding energy (kcal/mol)	Important amino acids involved (chain A)
1.	Rutaecarpine		–11.0	Leu338, ALA502, VAL509, SER339, VAL335, ALA513, LEU517
2.	Tryptanthrine		–10.9	VAL335, ALA513, VAL509, SER339, LEU517.
3.	Isolicoflavonol		–9.1	HIS75, TYR341, LEU345, VAL102, LEU517, VAL509, SER339, PHE504, ALA502, ALA513, VAL335
4.	Lonchocarpol A		–6.8	ASP333, HIS337, ASN567, PHE 566, PHE 563
5.	Curcumin		–9.1	LEU338, PHE504, ALA502, SER339, VAL509, VAL335, LEU517, TYR341, ALA513, SER516, TYR 371, GLY512
6.	Resveratrol		–9.1	HIS75, PHE504, VAL509, LEU338, VAL335
7.	Ursolic acid		–8.5	ASP33, LYS82, HIS342, GLY340, HIS337
8.	Celecoxib		–12.2	LEU345, VAL335, ALA513, TRP373, GLY512, TYR371, TYR341, VAL509, SER339, ARG449, HIS75, GLN178, LEU338, PHE504

The rutaecarpine with maximum binding energy showed pi sigma interaction between VAL509, SER339, and dihydro indole ring and another pi sigma interaction between VAL335 and ALA513 quinazoline and aryl ring, respectively. The flavonoid lonchocarpol A possessed the H-bond interaction between dihydroxy phenyl group and HIS337 and ASN567. The ursolic acid [Figure 4] (showing the docking posed of ursolic acid at the COX-2 site) possessed the H-bond between hydroxy group and GLY340 and ASP333. Figures 5 and 6 showing the docked possess of flavonoid.

The curcumin showed the three hydrogen bond with TYR371, SER516, and SER339 while flavonoid possessed two hydrogen bond

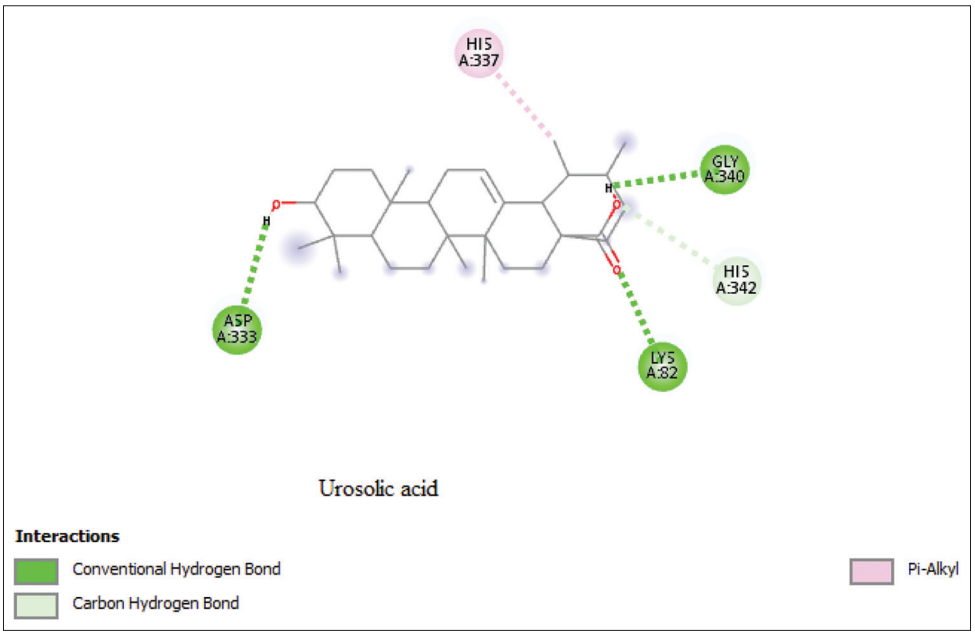


Figure 4: The interaction of ursolic acid at cyclooxygenase-2

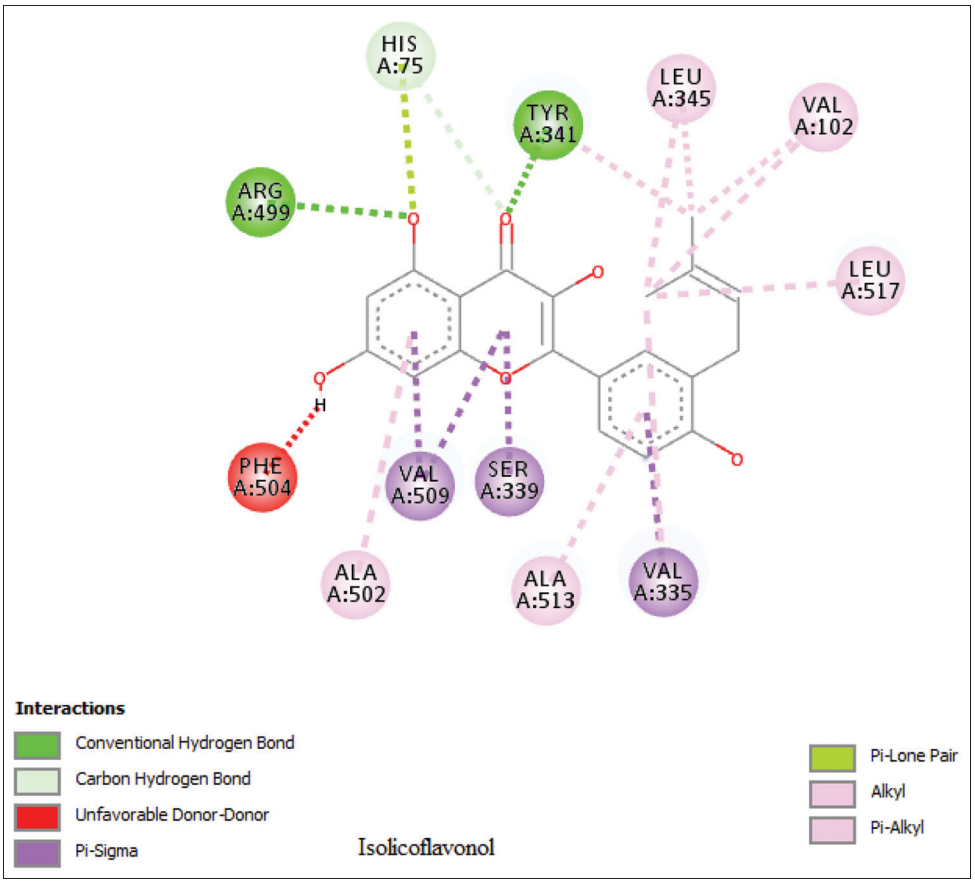


Figure 5: The interaction of isolicoflavonol at cyclooxygenase-2

with ARG449 and TYR341 with binding energy of –9.1 kcal/mol and resveratrol one hydrogen bond interaction with PHE504. Figures 7 and 8 showing the docking possess of resveratrol and curcumin at the COX-2 active site.

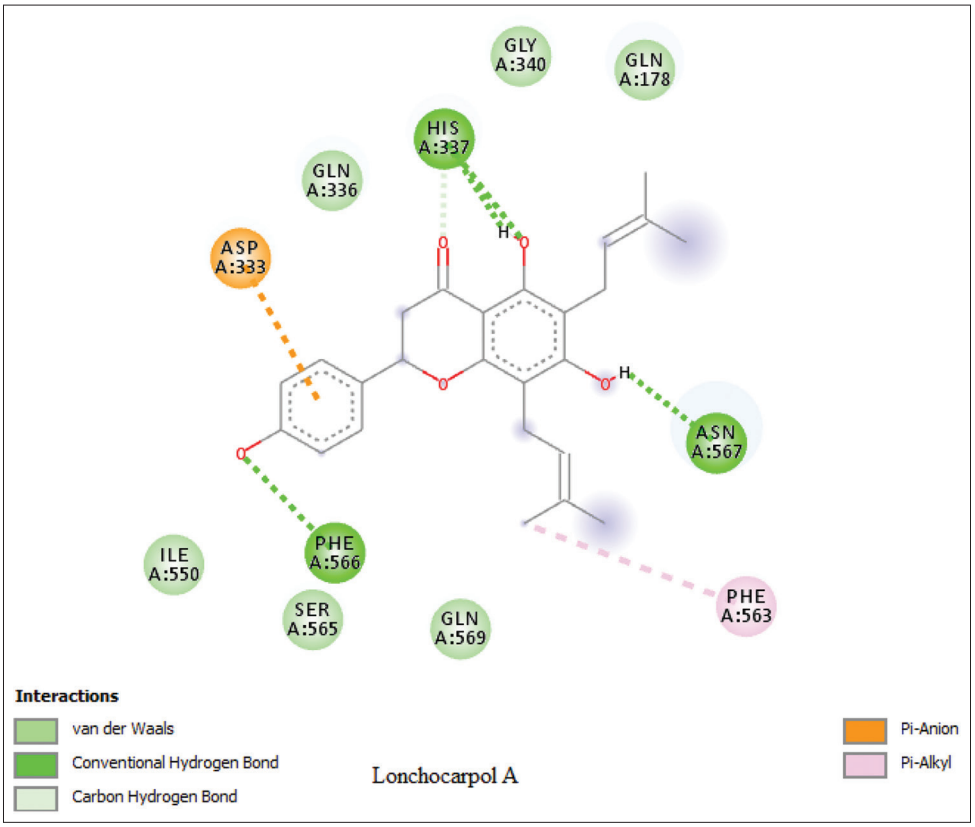


Figure 6: The interaction of lonchocarpol at cyclooxygenase-2

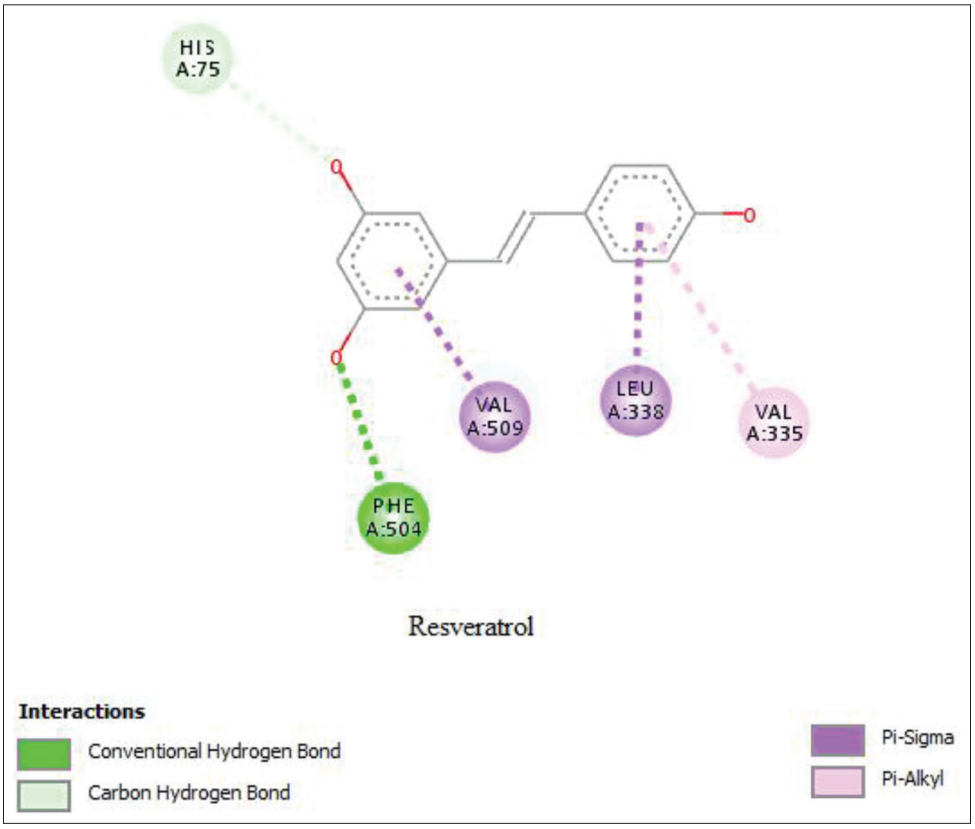


Figure 7: The interaction of resveratrol at cyclooxygenase-2

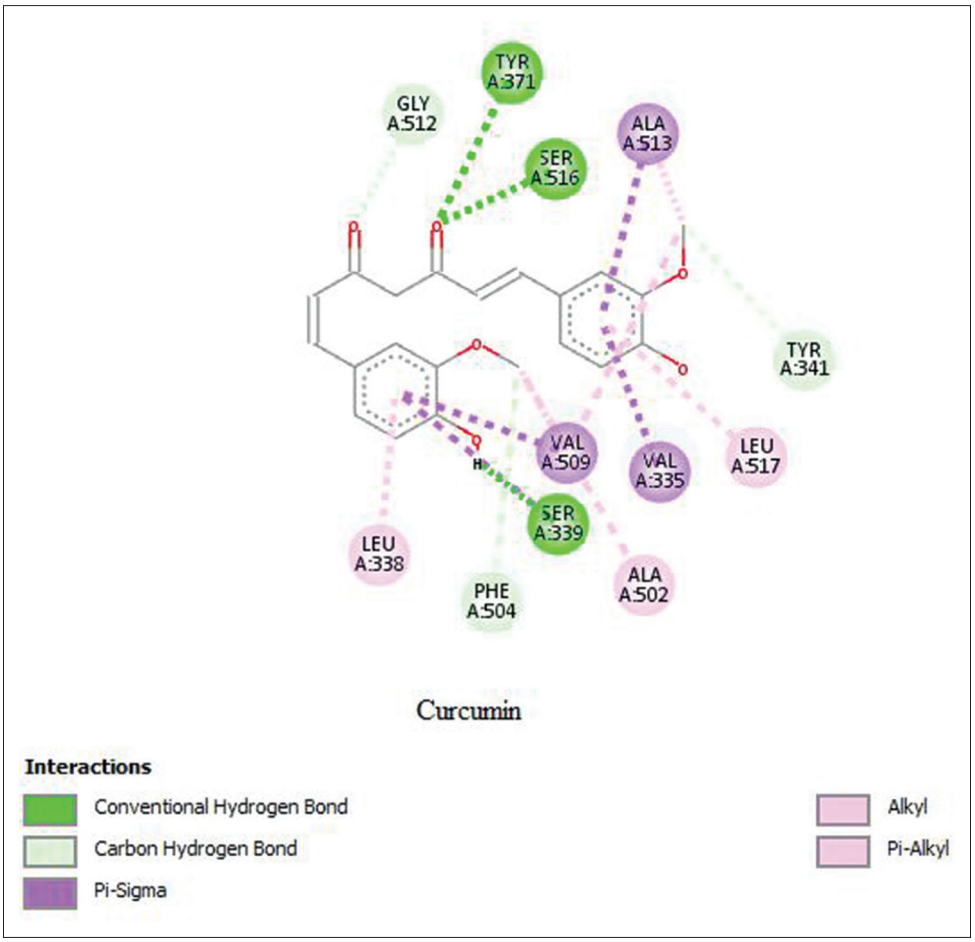


Figure 8: The interaction of curcumin at cyclooxygenase-2

These similarities in interaction of present studied compound with marketed compound celecoxib indicated that the natural compounds are able to occupy COX-2 active site effectively and be able to serve as a lead for the rational drug and design.

CONCLUSION

Selective COX-2 inhibitors exhibit anti-inflammatory properties by inhibiting COX-2 enzyme. Molecular docking study showed that the alkaloids (rutaecarpine and tryptanthrine) may behave like NSAIDs in regard to binding with the COX enzyme and may be used as an anti-inflammatory agent.

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